REMARKS

Applicants thank Examiners Robinson and Carlson for their time and helpful suggestions during the telephonic interview conducted with the undersigned on April 25, 2002, during which the rejections under 35 U.S.C. §112 were discussed. The substance of the interview is discussed below.

Claims 64, 69, 73, 81, 85, 89, 97, 100, 103, 113, 114, 116, 119, 120, 25, 130 and 135 have been amended. The amendments are supported throughout the application as filed, e.g., at page 19, lines 8-15, and Table 1 (pages 20-21). No new matter has been added. Claims 64-79, 81-94, 96-108, 110-120, 122-125, 127-130 and 132-135 are pending.

With respect to the telephonic interview conducted on January 23, 2002 with Examiner Robinson, Applicants note that box (i) in the Examiner's statement of the interview, mailed with the present office action, was not checked. For completeness of the record, Applicants' submit the following statement of the substance of the interview: Applicants agree with the Examiner's statement of the substance of the interview.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 64-79, 81-94, 96-108, 110-120, 122-125, 127-130 and 132-135 are rejected because "the specification, while being enabling for a synthetic nucleic acid encoding a protein, does not reasonably provide enablement for the any fragment thereof or portion thereof." This rejection has been met in part and is traversed in part.

Claims 64, 69, 73, 90, 97-98, 100, 102-104, 113, 114, 116, 119, 120, 25, 130 and 135 have been amended to remove the fragment language and to recite that the nucleic acid sequence encodes a human protein. It was discussed during the telephonic interview that the present amendments would obviate the rejection.

With respect to claims which recite human factor 8 protein (claims 81, 85 and 89), the fragment language has been replaced with "a functional portion thereof." Applicants note that the specification provides detailed guidance on how to make a synthetic nucleic acid that encodes a functional portion of [illegible]

(BDD factor 8). See, e.g., page 41, line 19 to page 42, line 29, and Figure 1. Therefore, functional portions of Factor 8 are fully enabled.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. §112, Second Paragraph

Claims 64-79, 81-94, 96-108, 110-120, 122-125, 127-130 and 132-135 are rejected as being indefinite because "the claims do not recite a specific sequence." It was agreed during the telephonic interview that this rejection should be withdrawn.

During the interview, the Examiner suggested that the term "common codon" was unclear because the claims did not specify for which organism the codon is common or non-common. The claims have been amended to specify what is meant by a common codon, as suggested by the Examiner during the telephonic interview. A discussion of common codons is found at pages 19-21, including Table 1, of the specification.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a Petition for Extension of Time with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 10278-009001.

Respectfully submitted,

Date: [illegible]

[signature]
Louis Myers
Reg. No. 35,965

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

Version with markings to show changes made

In the claims:

Claims 64, 69, 73, 81, 85, 89, 90, 97-98, 100, 102-104, 113, 114, 116, 119, 120, 25, 130 and 135 have been amended as follows:

64. (**Twice Amended**) A synthetic nucleic acid sequence which encodes a human protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence comprises a continuous stretch of at least 150 codons all of which are common codons, wherein [said continuous stretch encodes the protein or a fragment thereof] by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

69. (**Twice Amended**) A synthetic nucleic acid sequence which encodes a human protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence comprises a continuous stretch of common codons, which continuous stretch includes at least 60% or more of the codons in the synthetic nucleic acid sequence, wherein [said continuous stretch encodes the protein or a fragment thereof] by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

73. (**Twice Amended**) A synthetic nucleic acid sequence which encodes a human protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and wherein at least 98% or more of the codons in the sequence encoding the protein are common codons and wherein the protein is at least 100 amino acid residues in length, and

a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

81. (**Twice Amended**) A synthetic nucleic acid sequence which encodes human Factor VIII or a functional portion thereof, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of at least 150 codons all of which are common codons, wherein [said continuous stretch encodes the Factor VIII or a portion thereof] by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

85. (**Twice Amended**) A synthetic nucleic acid sequence which encodes human Factor VIII or a functional portion thereof, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least 60% of the codons of the synthetic nucleic acid sequence, [wherein said continuous stretch encodes the Factor VIII or a portion thereof] wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

89. (**Twice Amended**) A synthetic nucleic acid sequence which encodes human Factor VIII or a functional portion thereof, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein at least 98% or more of the codons in the sequence encoding the Factor VIII are common codons and the Factor VIII is at least 90 amino acid residues in length, and wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

90. (Amended) The synthetic nucleic acid sequence of claim 89 where the factor VIII protein has one or more of the following characteristics:

a) the B domain is deleted (BDD factor VIII);

b) it has a recognition site for an intracellular protease of the PACE/furin class; [or] and

c) it is expressed in a non-transformed cell.

97. (**Twice Amended**) A synthetic nucleic acid sequence which encodes human Factor IX, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of at least 150 codons all of which are common codons, [wherein said continuous stretch encodes the Factor IX or a portion thereof] and wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

98. (**Amended**) The synthetic nucleic acid sequence of claim 97, wherein the Factor IX protein has one or more of the following characteristics:

a) it has a PACE furin site at a pro-peptide mature protein junction; [or] and

b) is expressed in a non-transformed cell.

100. (**Twice Amended**) A synthetic nucleic acid sequence which encodes human Factor IX, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least 60% of the codons of the synthetic nucleic acid sequence, [wherein said continuous stretch encodes the Factor IX or a portion thereof] and wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

102. (**Amended**) The synthetic nucleic acid sequence of claim 100, wherein the factor IX protein has one or more of the following characteristics:

a) it has a PACE/furin site at a pro-peptide mature protein junction; [or] and

b) is expressed in a non-transformed cell.

103. (**Twice Amended**) A synthetic nucleic acid sequence which encodes human Factor IX, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein at least 98% or more of the codons in the sequence encoding the Factor IX are common codons and the Factor IX is at least 90 amino acid residues in length, and wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

104. (**Amended**) The synthetic nucleic acid sequence of claim 103, wherein the factor IX protein has one or more of the following characteristics:

a) it has a PACE furin site at a pro-peptide mature protein junction; [or] and

b) is expressed in a non-transformed cell.

113. (**Twice Amended**) A synthetic nucleic acid sequence which encodes a human

codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, and having the following properties:

(i) the synthetic nucleic acid sequence comprises a continuous stretch of at least 150 codons all of which are common codons[, wherein said continuous stretch encodes the protein or a fragment thereof];

(ii) the synthetic nucleic acid sequence comprises a continuous stretch of common codons, which continuous stretch includes at least 60% or more of the codons in the synthetic nucleic acid sequence[, wherein said continuous stretch encodes the protein or a fragment thereof]; and

(iii) wherein at least 98% or more of the codons in the sequence encoding the protein are common codons and wherein the protein is at least 90 amino acid residues in length.

114. (**Twice Amended**) A method for preparing a synthetic nucleic acid sequence which is at least 90 codons in length, comprising:

identifying a non-common codon and a less-common codon in a non-optimized gene sequence which encodes a human protein and is at least 90 codons in length; and

replacing at least 98% of the non-common and less-common codons with a common codon encoding the same amino acid residue as the replaced codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

116. (**Twice Amended**) A method for making a nucleic acid sequence which directs the synthesis of an optimized message of a human protein of at least 90 amino acids comprising:

synthesizing at least two fragments of a nucleic acid sequence, wherein the two fragments encode adjoining portions of a human protein of at least 90 amino acids and wherein both fragments are mRNA optimized; and

joining the two fragments such that a non-common codon is not created at a

119. (**Twice Amended**) A method for preparing a synthetic nucleic acid sequence encoding a human protein which is at least 90 amino acid residues in length, comprising identifying non-common codon and less-common codons in the non-optimized nucleic acid sequence encoding a protein of at least 90 amino acid residues in length and replacing at least 98% or more of the non-common and less-common codons of the nucleic acid sequence encoding the protein with a common codon encoding the same amino acid residue as the replaced codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, thereby preparing a synthetic nucleic acid sequence encoding a human protein which is at least 90 amino acid residues in length.

120. (**Twice Amended**) A primary or secondary mammalian cell having an exogenous synthetic nucleic acid sequence which encodes a human protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, and wherein the synthetic nucleic acid has a continuous stretch of at least 150 codons all of which are common codons[, wherein said continuous stretch encodes the protein or a portion thereof]; is at least 80 base pairs in length; and is free of unique restriction endonuclease sites in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the human protein or polypeptide product.

125. (**Twice Amended**) A primary or secondary mammalian cell having an exogenous synthetic nucleic acid sequence which encodes a human protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding

expressed human genes as shown in Table 1, and wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least 60% of the codons of the synthetic nucleic acid sequence, [wherein said continuous stretch encodes the protein or a portion thereof;] is at least 80 base pairs in length and is free of unique restriction endonuclease sites in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the human protein or polypeptide product.

130. (**Twice Amended**) A primary or secondary mammalian cell having an exogenous synthetic nucleic acid sequence which encodes a human protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, and wherein at least 98% or more of the codons in the sequence encoding the protein are common codons and the protein is at least 90 amino acids in length; [it]the nucleic acid sequence is at least 80 base pairs in length and is free of unique restriction endonuclease sites in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the human protein or polypeptide product.

135. (**Twice Amended**) A primary or secondary mammalian cell having an exogenous synthetic nucleic acid sequence which encodes a human protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, wherein by a common

following properties: it has a continuous stretch of at least 150 codons all of which are common codons[, wherein said continuous stretch encodes the protein or a portion thereof]; it has a continuous stretch of common codons which comprise at least 60% of the codons of the synthetic nucleic acid sequence[, wherein said continuous stretch encodes the protein or a portion thereof]; at least 98% or more of the codons in the sequence encoding the protein are common codons and the protein is at least 90 amino acids in length; it is at least 80 base pairs in length and which is free of unique restriction endonuclease sites in the message optimized sequence; and

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the human protein or polypeptide product.